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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,258	09/25/2003	Robert O. Williams	10071-037-999	3229

20582 7590 03/31/2009

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EXAMINER	
ROYDS, LESLIE A	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
03/31/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,258	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *1-23,28,40-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-27,29-39,58* is/are rejected.

7)☒ Claim(s) *24,27 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *25 Sept 03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-58 are presented for examination.

Acknowledgment is made of the present application as a proper continuation (CON) application of U.S. Patent Application No. 09/931,293, filed August 17, 2001, now issued as U.S. Patent No. 6,638,981.

Applicant's Information Disclosure Statement (IDS) filed September 25, 2003 (four pages total) has been received and entered into the present application. As reflected by the attached, completed copy of form PTO-1449, the Examiner has considered the cited references, with the exception of the cited non-patent literature references on the IDS filed September 25, 2003. Applicant refers to the previously submitted copies of these documents in prior U.S. Patent Application No. 09/931,293. However, after a reasonable search by the Examiner, said documents could not be located and, therefore, have not been further considered.

Applicant's response filed July 10, 2007 to the requirement for restriction/election dated January 10, 2007 has been received and entered into the present application. Pursuant to the notice dated October 5, 2007, Applicant's response of July 10, 2007 was held to be non-compliant. Applicant's supplemental response filed October 30, 2007 correcting the deficiencies identified in the notice of October 5, 2007 has also been received and entered into the present application. However, the response filed October, 5, 2007 was also non-compliant pursuant to the notice sent January 28, 2008. Applicant's response filed April 28, 2008 was received and entered into the present application, but the requirement for restriction/election dated January 10, 2007 was vacated in lieu of the new requirement dated July 14, 2008. Applicant's response filed January 14, 2009 was received and entered into the present application.

Requirement for Restriction/Election

Applicant's election **without traverse** of the invention of Group II (claims 24-40 and 58),

directed to a method for treating pain comprising topically administering to the skin of a mammal in need thereof an emulsion comprising an antidepressant, an NMDA receptor antagonist, a lipophilic component, water and a surfactant, and the species of (a) amitriptyline as the antidepressant; (b) ketamine as the NMDA receptor antagonist; (c) petrolatum as the lipophilic component; (d) PEG-100 stearate as the surfactant; (e) TRANSCUTOL P (ethoxydiglycol) as the lipophilic intradermal penetration enhancer; and (f) simethicone as the antifoaming agent; in the replies filed July 10, 2007 and October 30, 2007, is acknowledged by the Examiner.

It is noted that the election of an antifoaming agent is understood as an election that a humectant agent is NOT present in the instantly claimed emulsion, since the requirement for restriction/election dated July 14, 2008 only provided for EITHER a humectant OR an anti-foaming agent to be present in the claimed emulsion. Accordingly, election of the anti-foaming agent simethicone is an implicit admission that a humectant is NOT present in the instantly claimed emulsion, though not explicitly stated on the record by Applicant.

Upon further reconsideration of the instant claims, the requirement for an election of species of (a) lipophilic component and (b) surfactant are each hereby **withdrawn**.

Therefore, for the reasons above and those made of record at p.2-12 of the previous Office Action dated July 14, 2008, the requirement remains proper and is hereby made **FINAL**.

Claims 1-23, 28 and 40-57 are **withdrawn** pursuant to 37 C.F.R. 1.142(b) as being drawn to non-elected subject matter.

The claims corresponding to the elected subject matter are claims 24-27, 29-39 and 58 and such claims are herein acted on the merits.

Objection to the Claims

Claim 24 is objected to for failing to define the acronym "NMDA" at its first occurrence in the

claims.

Claim 27 is objected to for failing to define the acronyms "HT" and "NK1" at their respective first occurrence in the claims.

Claim 33 is objected to for failing to define the acronym "PCP" at its first occurrence in the claims.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-27, 29-39 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, Applicant's instant claim 24 recites, "…comprising topically administering to the skin of a mammal in need thereof an emulsion…". However, it is unclear if it is the skin or the mammal that is, in fact, in need of topical administration of the instantly claimed emulsion. Specifically, the claim fails to clearly set forth what is in need of the topically applied emulsion, i.e., either a specific portion of skin or the mammal *per se*. For example, it is unclear if the skin is experiencing pain and would require topical application of the instantly claimed emulsion to treat said pain or if the mammal is experiencing pain and would require topical application of the instantly claimed emulsion to treat said pain.

Furthermore, the antecedent basis for the phrase "in need thereof" as recited in independent claim 24 is unclear because the claims do not specifically set forth whether the phrase "in need thereof" limits the patients to be treated to (1) either skin or mammal(s) that is in need of treatment of pain or (2) either skin or mammal(s) that are in need of the instantly claimed emulsion. For this reason, the claims fail to clearly, deliberately and precisely set forth what or whom is to be treated in the instantly claimed method.

Accordingly, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the scope of the subject matter for which Applicant is presently seeking protection. Clarification is requested.

Claims 24-27, 29-39 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, instant claim 24 recites "a therapeutically effective amount of an NMDA receptor antagonists", which is indefinite. The term "an" is indicative of a single antagonist, but the term "antagonists", which follows the term "an" in the claim, circumscribes more than one antagonist. Accordingly, the terms conflict and it is not clear as to which term is meant to limit the instant claims (i.e., either a single antagonist or plural antagonists). As a result, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the scope of the subject matter for which Applicant is presently seeking protection. Clarification is requested.

Furthermore, instant claims 33-35 each recite the limitation "the NMDA receptor antagonist" in line 1 of each of the claims. Such a limitation lacks clear antecedent basis because the preceding claims only provide for "an NMDA receptor antagonists". Again, as above, it is unclear whether the instant claims are meant to circumscribe the use of a single NMDA receptor antagonist or multiple NMDA receptor antagonists and, thus, the intended antecedent basis for the limitation "the NMDA receptor antagonist" as recited in each of claims 33-35 is not clearly set forth. As a result, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the scope of the subject matter for which Applicant is presently seeking protection. Clarification is requested.

Claims 30 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for

failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Regarding claim 30, the recitation of the phrase "or a pharmaceutically acceptable salt thereof" in line 7 of instant claim 30 does not clearly, precisely or deliberately set forth whether the phrase modifies the compound that directly precedes it (i.e., use of a pharmaceutically acceptable salt of tianeptine) or whether it is intended to circumscribe the use of a pharmaceutically acceptable salt of *any* one of the compounds recited in the claim. As a result, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection. Clarification is requested.

Similarly, regarding claim 35, the recitation of the phrase "or a pharmaceutically acceptable salt thereof" in line 7 of instant claim 35 does not clearly, precisely or deliberately set forth whether the phrase modifies the compound that directly precedes it (i.e., use of a pharmaceutically acceptable salt of 6,7-dinitro-quinoxaline-2,3-dione) or whether it is intended to circumscribe the use of a pharmaceutically acceptable salt of *any* one of the compounds recited in the claim. As a result, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection. Clarification is requested.

Claims 32 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Regarding claim 32, the phrase "an amount of the antidepressant" in line 1 of the claim is unclear because the claim fails to clearly set forth whether this "amount" in instant claim 32 is the same as the "therapeutically effective amount" as recited in instant claim 24 or if it circumscribes *any* amount of antidepressant. As a result, one of ordinary skill in the art at the time of the invention would not have

been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection. Clarification is requested.

Regarding claim 37, the phrase "an amount of the NMDA receptor antagonist" in lines 1-2 of the claim is unclear because the claim fails to clearly set forth whether this "amount" in instant claim 37 is the same as the "therapeutically effective amount" as recited in instant claim 24 or if it circumscribes *any* amount of NMDA receptor antagonist. As a result, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection. Clarification is requested.

Claims 33-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, the phrase "or a pharmaceutically acceptable salt thereof" is unclear because it fails to clearly set forth whether it is intended to modify the "NMDA receptor antagonist" (i.e., and, thus, be a pharmaceutically acceptable salt of the NMDA receptor antagonist) or whether it is intended to modify the receptor site to which the antagonist binds (e.g., a pharmaceutically acceptable salt of the PCP binding site). Accordingly, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection. Clarification is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24-27, 29-39 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ford (U.S. Patent No. 6,461,600; Issued October 2002, Filed July 2001) in view of Remington's Pharmaceutical Sciences (Fifteenth Edition; 1975; p.327-339, 1452-1456).

Ford teaches a topical pain relief composition and carrier, comprising squalene NF, an emulsifier such as TWEEN 80, glycerin, cetyl alcohol NF, glyceryl monostearate (i.e., meets Applicant's limitation directed to a "surfactant" as in instant claim 24 per Applicant's definition of "surfactant" at p.19 of the instant specification, which is defined as, *inter alia*, glyceryl monostearate), lecithin organogel preserved, BHT, urea USP, EDTA, water, stearic acid (i.e., meets Applicant's limitation directed to a "lipophilic component" as in instant claim 24 per Applicant's definition of "lipophilic component" at p.17 of the instant specification, which is defined as, *inter alia*, stearic acid), simethicone USP as an anti-foaming agent (instant claim 58), ethoxydiglycol (i.e., Applicant's elected species of lipophilic intradermal penetration enhancer), wherein the carrier is in combination with either or both of ketamine hydrochloride (i.e., Applicant's elected species of NMDA receptor antagonist; note also that Applicant defines ketamine at p.16 of the instant specification as an NMDA receptor antagonist that binds at the PCP site as required by instant claims 33-34) and amitriptyline hydrochloride (i.e., Applicant's elected species of antidepressant, specifically, a tricyclic antidepressant), which are each topically applied analgesic compounds (abstract). Ford further teaches that the composition comprises the above-described carrier

with the two active ingredients, wherein ketamine hydrochloride is present in an amount of between 3 mg/ml and 150 mg/ml (with a preferred amount of 5 mg/ml of carrier) and amitriptyline hydrochloride in an amount of between 5 mg/ml and 20 mg/ml (with a preferred amount of 10 mg/ml of carrier) (col.2, l.7-12). Ford discloses that the preparations according to the instant invention are suitable for treating pain and pain-related conditions, including intractable pain that is non-responsive to opioids, myofascial pain, postherpetic neuralgia, neuropathic pain, etc. (col.3, l.65-col.4, l.9).

Ford fails to teach (1) that the disclosed preparation is an oil-in-water emulsion (claim 24), (2) that the emulsion has a mean oil droplet size of about 0.01 microns to about 100 microns (claims 25-26) or (3) that the antidepressant and the NMDA receptor antagonist are each present in an amount of about 0.1% by weight to about 10% by weight of a total weight of the emulsion (claims 32 and 37).

Remington's Pharmaceutical Sciences is cited for its teachings that the majority of conventional emulsions in pharmaceutical use have dispersed particles ranging in diameter from 0.1-100 microns (col.1, para.2, p.327). Remington's also teaches that compounds with an HLB range of from 8-18 are used as O/W emulsifying agents and those with an HLB value of from 10-18 are also effective solubilizing agents (Table VI, p.334). Further, Remington's discloses that the compound TWEEN 80 (also known as polyoxyethylene sorbitan monooleate) has an HLB value of 15.0 (Table VII, p.335) and stearic acid has an HLB value of 17.0 for O/W emulsions (Table VIII, p.336).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious that the disclosed preparation of Ford would have been, specifically, an oil-in-water (O/W) emulsion because, as evidenced by Remington's, the use of agents with HLB values between 8-18 are effective to form O/W emulsions and at least two of the emulsifying agents used in the composition of Ford have high HLB values suggestive of their activity as O/W emulsifying agents (i.e., HLB of TWEEN 80=15.0 and HLB of stearic acid=17.0). Such teachings clearly raise the reasonable expectation of

success that the final product of the formulation disclosed by Ford would have been in the form of an O/W emulsion, as instantly claimed, absent factual evidence to the contrary.

Furthermore, though the mean oil droplet size of 0.1-100 microns is not explicitly disclosed by Ford, one of ordinary skill in the art would have found it *prima facie* obvious to employ such a mean oil droplet size in the final emulsion of Ford because, as evidenced by Remington's, such a mean droplet size of the dispersed phase (which, for an O/W emulsion would be the oil droplet size) is between 0.1-100 microns for pharmaceutically purposeful emulsions. Such a person would have been motivated to use such a mean droplet size for the oil phase of the disclosed emulsion of Ford because Remington's teaches that such a mean oil droplet size is conventionally used to form an emulsion that is pharmaceutically acceptable (which, for the reasons described *supra*, the emulsion of Ford is pharmaceutically acceptable for topical application for the treatment of various types of pain and pain-related conditions).

Regarding the instantly claimed amounts of the antidepressant and/or NMDA receptor antagonist component(s) (as in instant claims 32 and 37), the determination of the optimum dose of the active amitriptyline and/or ketamine compound(s) would have been a matter well within the purview of one of ordinary skill in the art and would have been made in accordance with a variety of factors, including, but not limited to, the dosage amount(s) to be administered based on the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and adverse reactions, patient tolerability to the regimen, desired time to onset of therapeutic effect, desired duration of therapeutic effect, etc.. Thus, the optimal dose that would have actually been employed would have varied in accordance with these factors and, in the absence of evidence to the contrary, is not seen to be inconsistent with that which would have been readily and easily determined by the skilled artisan using routine experimentation.

Conclusion

Rejection of claims 24-27, 29-39 and 58 is proper.

Claims 1-23, 28 and 40-57 are **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

March 18, 2009

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614